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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,855	11/02/2005	Patrick Van Berkel	089995-000000US	4048

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,855	BERKEL ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-9,13,16,17,19,20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6-9, 13, 16-17, 19-20, and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/13/2009 has been entered.

Applicant's response filed on 10/13/2009 in response to office action mailed on 04/13/2009 has been acknowledged.

Claims 1-10, 13, 16, and 21 are amended.

Claims 2, 3, 5 10, 12, 18, and 21 are canceled.

Claims 11, 12, 14-15 were previously cancelled.

Claims 23-27 are new.

Claims 1, 4, 6-9, 13, 16-17, 19-20, and 22-27*are pending and are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Withdrawn: Claims 1-10, 13 and 16-22 are rejected under 35 USC 103 (a) as being unpatentable over Paulson et al (1998, WO 98/31826), Shoenberger et al (1992, FEBS 314: 430-434), Wolf et al., (2001, protein expression and purification 22:414-421) and in view of Glaser et al (WO 92/03149) and Lamark et al (2001, Protein expression and Purification 22:349-358; art of record) for the reason of record as set forth in the office action mailed 04/13/2009 is withdrawn in view of Applicants amendments and further in view of a new 35USC103 rejection below .

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1, 4, 6-9,13,16-18, 19-20, and 22-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant human C1 inhibitor that is changed in its circulatory half-life by a O-linked carbohydrate modification in vitro on O-linked carbohydrate moieties Gal or Gal (β1-3)Gal(NAC) and using the O-linked carbohydrate modifying enzymes ST3Gal I and/or ST3Gal III, is not enabled for any O-linked carbohydrate modifying enzymes, is not enabled for any modified O-linked carbohydrate for increasing the circulatory half life of said human recombinant C1 inhibitor or for changing the circulatory half-life of a human C1 inhibitor in vivo as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. “Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through ‘’undue experimentation” in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope of invention as claimed encompasses compositions or products of a recombinant human C1 inhibitor that is modified in its O-linked glycosylation site using any modifying enzyme and sialylating any O-linked carbohydrate with a terminal galactose residue.

However applicant does not disclose representative enabled examples of any broadly claimed recombinant C1INH protein O-glycosylation other than with the carbohydrate moieties Gal or Gal (β1-3)Gal(NAC) or scialylation modifying enzymes other than ST3Gal I and ST3Gal III for increasing the half-life of C1 inhibitor in vivo or in any cultured cell, further does not enable the breadth of the claims that encompass sialylation of any carbohydrate. In the absence of representative number of enabled examples several subgenus of enzymes encompassed by the claim it would require undue experimentation to practice the invention in its full scope.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

***Guidance of the Specification, Existence of Working Examples, State of the Art and the Predictability of the Art*:** With respect to invention instant specification only provides guidance and/or evidences regarding use of an a recombinant C1 inhibitor (rhC1INH) that is scialylated on O-linked carbohydrate moieties Gal (β1-3)Gal(NAC) in vitro with O-linked carbohydrate modifying enzymes ST3Gal I, ST3Gal II and intravenously injecting test the same for an increased half-life in plasma circulation. Further the specification does not enable any other O-linked carbohydrates or carbohydrate modifying enzymes other than ST3Gal I and ST3Gal III that to increase the circulatory half life of the human C1 inhibitor. Given the lack of predictability in the prior art regarding the functions of various carbohydrates chains that can be removed or introduced and scialylated by modifying enzymes how one of skill in the art would be able to obtain therapeutic C1INH without affecting its functional specificity in vivo. Art at the time of invention indicates that the central question of how glycosylation contributes

to the glycoprotein structure and function is not yet clear (Wang et al., 1996, Biochemistry 35:7929-7307, entire article, abstract; p.7299, col.2 bridging p.7300). Different glycosylation moieties introduced by different enzymes or chemical attachments may cause various specific effects such as intracellular traffic and localization of protein, modification of immunological properties and other properties apart from increasing circulatory half-life of a protein or the stability of the proteins. Thus with the upredictability of the art regarding the role of glycosylations coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the invention as claimed i.e., using any O-linked carbohydrates and using any carbohydrate scialylation modifying enzymes to change the stability of the protein. Further art teaches that certain scialylating moieties are specific to species and may cause severe immunological reactions in other species (example NeuGc substitution is antigenic in humans see WO 98/31826, p.2, line 4-12). Thus one of skill in the art would not predict what kind of change is brought about by different carbohydrates or carbohydrate modifying enzymes.

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the specific effects of modifying O-glycosylation of C1 inhibitor by different carbohydrates and their terminal galactose residue sialylation modifying enzyme. One of skill in the art have to experiment with different glycosylating deglycosylating enzymes and those with specificity for different sugar moieties and test the so modified human C1 inhibitor samples for stability in the circulation in live animals or animals. However, one of skill in the art would be confused if these introduced modifications in O-linked sugars bring in any other effects on the modified protein in terms of its specificity, localization or immune reactions etc. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enablement of sufficient number of examples broadly claimed glycosylation modifying enzymes as of around the filing date of instant application and for the specific reasons

cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention.

Response to Arguments of 10/13/2009:

Applicant amends claims to reflect sialylation modifications restricted to terminal galactose residue on O–linked carbohydrate moiety. Applicant argues therefore concerns over the enablement of the scope of the claim encompassing in vivo modulation of half-life of recombinant CINH with any O-linked glycosylation.

Applicants' arguments are however, found not persuasive because firstly the primary Claims encompasses in its breadth extending circulatory half-life of a recombinant C1INH by scialylating with any scialylatin moiety with any scilaylating enzymes and modifying terminal galactose of any of O-linked glycosylation moiety. However applicant does not disclose representative enabled examples of any broadly claimed recombinant C1INH protein O-glycosylation other than with the carbohydrate moieties Gal or Gal (β1-3)Gal(NAC) or scialylation modifying enzymes other than ST3Gal I and ST3Gal III for increasing the half-life of C1 inhibitor in vivo or in any cultured cell, further does not enable the breadth of the claims that encompass sialylation of any carbohydrate. In the absence of an enabled examples and/or a representative number of enabled examples in the specification regarding specificity of modulation by representative number of species of various sub genus of O-linked glycosylation enzymes used for modifying a therapeutic protein such as C1 inhibitor or other protein one of ordinary skill in the art would conclude that the invention as instantly claimed is unpredictable and 'undue'. Hence the rejection is maintained with modifications and extended to new claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 6-9, 13, 16-17, 19-20, and 22-27 are rejected under 35 USC 103 (a) as being unpatentable over Wolf et al., (2001, protein expression and purification 22:414-421) and Paulson et al (1998, WO 98/31826).

The above claims are directed to a recombinant C1-inhibitor that is changed with regard to its plasma circulatory half-life by modification of an O-linked carbohydrate by an O-linked carbohydrate modifying enzyme in vitro wherein the modified O-linked carbohydrate comprises a sialylated terminal glactose residue.

Wolf teaches regarding production and purification of recombinant C1 inhibitor and the various glycosylations levels of C1INH (p.415, col.1, 2nd paragraph). Wolf further teaches the differences between native and recombinant molecules in terms of their glycosylation and the importance of reduced O-glycosyaltion in hereditary diseases involving (p.419, col.2, 2nd paragraph). He further indicates engineered glycosylation pathways to obtain recombinant inhibitor (rC1INH) for clinical evaluation (p.420, col.1). Wolf however, does not teach extending the circulatory half-life or reducing the clearance rate by sialylating the terminal galactose residue of the O-linked carbohydrates on C1 INH protein in vitro.

Regarding claims 1-6 and Paulson teaches increasing plasma circulatory half life or decreasing the circulatory clearance rates of various therapeutic proteins including various serum proteins (to which the instantly claimed C1INH belongs to) that have been produced by recombinant method by modifying both N- and O-glycosylation moieties (Abstract, p.1, lines 20-25, p.2, 3rd paragraph; p.8, 2nd paragraph; p.25, lines 5-10; Table 5) by scialylation (p.1, lines 20-25; p.2, 4th paragraph brdging p.3). Regarding claims 7-9 Paulson teaches use of one or more enzymes including ST3 gal I, ST3 Gal III etc., (p.3, 2 and 3rd paragraph and p.18, Examples). Regarding claim 10-12 Paulson teaches various recombinant glycoproteins that are modified in vitro sialylation (p.7, 2nd, 3rd and 4th paragraph bridging p.8, and p.25) and pathways to obtain a recombinant inhibitor (rC1INH) for clinical evaluation (p.420, col.1). Reasons to believe otherwise Paulson's recombinant protein preparations with their O-glycosylation sites modified

with their sialylated terminal galactose residues have their circulatory half-life extended or circulatory clearance rates decreased..

Thus it would have been obvious for one of ordinary skill in the art to incorporate into Wolf's method and compositions of making a recombinant C1INH for clinical evaluation a step of modifying the O-linked carbohydrate by scialylation of their terminal galactose residues as taught by Paulson and decrease their clearance rate in circulation and thereby increasing the circulatory half-life of the recombinant unmodified C1INH. One of skill in the art would have been motivated to increase the circulatory stability or circulatory half-life of a recombinant therapeutic serum protein, at least to the extent of normal protein, by sialylating the glycosylated sites as it would reduce the dosage and/or delivery frequency of the therapeutic protein for treating subject in need and thereby increase the efficacy of treatment. One of skilled in the art would be motivated to do so for treating a disease related to reduced C1 inhibitory activity by providing a recombinant C1 protein that has been appropriately modified to increase its plasma circulatory half life, at least closer to that observed for normal protein, by appropriately scialylating N and/or O-linked carbohydrate moieties on the protein because the art teaches it is routine to produce a recombinant human C-1 inhibitor or other serum proteins, often without proper glycosylation modifications, for therapeutic purposes and art further teaches that it is routine to sialylate terminal galactose residues of N- and/or O-linked carbohydrates to increase their half-life (or decrease their clearance rate in the circulation) comparable to that of a normal human C1INH. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/

Primary Examiner, Art Unit 1633